PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post

PCT

To:

BAKER, Hollie L. et al
HALE AND DORR LLP
60 State Street
Boston, Massachussetts 02109
ETATS-UNIS D'AMERIQUE

Fax: 617 526 5000

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	15.12.2000
Applicant's or agent's file reference: 686.03.498	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27505	19/11/1999	19/11/1998

International Patent Classification (IPC) or both national classification and IPC

C12N5/06

Applicant

ORGANOGENESIS INC. et al.

Docketed 15Feb01
By LD on 20Dec00

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 19/03/2001.

HALE AND DORR LLP
DEC 20 2000
DOCKET DEPT.
INTELLECTUAL PROPERTY DEPARTMENT

Name and mailing address of the International preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Heckl, K

Formalities officer (incl. extension of time limits)

Emslander, S

Telephone No. +49 89 2399 8718

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-49 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-18,27,28part,30 part,

because:

☒ the said international application, or the said claims Nos. 16-18,27,28part,30 part relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☒ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 16-18,27,28part,30 part.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	16-18,27,28part,30 part
Inventive step (IS)	Claims	16-18,27,28part,30 part
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Industrial applicability (Art.33(4) PCT)

Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art.34(4)(a)(i) PCT).

For the assessment of the present claim 28 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

1. The International search report has been drawn up in respect of the entire international application but the International Preliminary Examining Authority is of the opinion that the application does not comply with the requirements of unity of invention as set forth in the PCT regulations (Article 34(3), Rules 13 and 68 PCT):

2. The separate inventions/groups of invention are:

   (i) a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar collagen, decorin and glycosaminoglycans (claims 1-7),

(ii) a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans (claim 8)

(iii) a cultured tissue construct having at least two layers comprising the cultured tissue construct of subject-matter (i), and having a second layer of cells comprising epithelial cells deposited on the first layer (claims 9-15)

(iv) a cultured skin which having at least two layers, wherein the first layer is comprised of fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, the second layer consisting of keratinocyte cells disposed on the first layer, and having a basement membrane present at the junction of the first and second layer (claims 16-18)

(v) a method of producing the cultured tissue construct of subject-matter (i) wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel (claims 19-23)
(vi) a method of producing a bilayered cultured tissue construct which construct seems to comprise the construct of subject-matter (i), wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel, and a second layer of epithelial cells (claims 24-26)

(vii) a method of producing a bilayered cultured skin construct comprising a dermal and an epidermal layer wherein fibroblasts are cultured to form a layer of synthesized extracellular matrix, the extracellular matrix comprising fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, and wherein the cultured skin construct has a basement membrane present at the junction of the first and second layer

(claim 27)

(viii) a method of producing a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar collagen, tenascin and glycosaminoglycans, and wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel (claim 29);

and claims 28 and 30 partially, i.e. as far as referring to each of the above identified groups.

3. They are not so linked as to form a single general inventive concept for the following reasons:

The common concept linking together the independent claims is the culturing of fibroblast cells in the absence of exogenous matrix components or synthetic members thereby leading to the formation of a self-supporting extracellular matrix. This is concept is well known from EP-A-0 282.764 (D1, see col.4, line 3 to col.6, line 9).

4. With the letter dated 14.11.00, the Applicant requested subject-matter (iv) and (vii) to be subjected to IPE. The Applicant payed two additional fees. To get two inventions subjected to IPE, the Applicant had to pay only one additional fee. Therefore, the second additional fee will be refunded upon request.

5. Hence, claims 16-18, 27 (complete) and claims 28 and 30 partially, i.e. as far as referring to each of the above identified groups are subjected to IPE.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

D1: EP-A-0 282 746

2. Two inventions are subjected to IPE:

subject-matter(iv) concerning a cultured skin which having at least two layers, wherein the first layer is comprised of fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, the second layer consisting of keratinocytes cells disposed on the first layer, and having a basement membrane present at the junction of the first and second layer (claims 16-18) and

subject-matter (vii) concerning a method of producing a bilayered cultured skin construct comprising a dermal and an epidermal layer wherein fibroblasts are cultured to form a layer of synthesized extracellular matrix, the extracellular matrix comprising fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, and wherein the cultured skin construct has a basement membrane present at the junction of the first and second layer (claim 27)

3. Novelty (Art.33(2) PCT):

D1 discloses an artificial cultured tissue and its production consisting of one type of cells (see claims 1-15).

In the view of D1 (and of the other cited prior art) the subject-matter of claims 16-18 (subject-matter (iv) and of claim 27 (subject-matter (vii)) appears novel. The same applies to claims 28 and 30 as far as referring thereto.

4. Inventiveness (Art.33(3) PCT):

It is noted that nowhere in the cited prior art cultured tissues having at least two layers and having a basement membrane present at the junction of the first and second layer have been suggested. In addition, the particular compositions of the first layer which is in the case of subject-matter (iv) fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans and in the case of subject-matter (vii) fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, are also not rendered obvious.

Accordingly, the subject-matter of claims 16-18 and 27 comprises an inventive step. The same applies to claims 28 and 30 as far as referring thereto.

Re Item VIII

Certain observations on the international application

The independent claims do not disclose how the particular composition of the first layer can be achieved. Being the basis for the acknowledgement of inventive step, these features are considered essential to the present invention and as such are to be included into the independent claims (Art.6 Pct, lack of clarity)

PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BAKER, Hollie L. et al
HALE AND DORR LLP
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Boston, Massachussetts 02109
ETATS-UNIS D'AMERIQUE

FAX NO: 617 526 5000

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06.02.2001
Applicant's or agent's file reference 686.03.498	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27505	19/11/1999	19/11/1998

Applicant
ORGANOGENESIS INC. et al.

Docketed 06 May 01 – File Supp IDS?
By UD on 14 Feb 01

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

HALE AND DORR LLP
FEB 12 2001

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
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Authorized officer

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DOCKET DEPT. INTELLECTUAL PROPERTY DEPARTMENT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
686.03.498		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27505	19/11/1999	19/11/1998
International Patent Classification (IPC) or national classification and IPC C12N5/06		
Applicant ORGANOGENESIS INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/06/2000	06.02.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Heckl, K
Telephone No. +49 89 2399 8430

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27505

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-49 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1-5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16-18,27,28part,30 part.

because:

☒ the said international application, or the said claims Nos. 16-18,27,28part,30 part relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☒ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 16-18,27,28part,30 part.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16-18,27,28part,30part
	No:	Claims	
Inventive step (IS)	Yes:	Claims	16-18,27,28part,30part
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	16-18,27,30part
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Industrial applicability (Art.33(4) PCT)

Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art.34(4)(a)(i) PCT).

For the assessment of the present claim 28 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

1. The International search report has been drawn up in respect of the entire international application but the International Preliminary Examining Authority is of the opinion that the application does not comply with the requirements of unity of invention as set forth in the PCT regulations (Article 34(3), Rules 13 and 68 PCT):

2. The separate inventions/groups of invention are:

   (i) a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar collagen, decorin and glycosaminoglycans (claims 1-7),

(ii) a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans (claim 8)

(iii) a cultured tissue construct having at least two layers comprising the cultured tissue construct of subject-matter (i), and having a second layer of cells comprising epithelial cells deposited on the first layer (claims 9-15)

(iv) a cultured skin which having at least two layers, wherein the first layer is comprised of fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, the second layer consisting of keratinocyte cells disposed on the first layer, and having a basement membrane present at the junction of the first and second layer (claims 16-18)

(v) a method of producing the cultured tissue construct of subject-matter (i) wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel (claims 19-23)
(vi) a method of producing a bilayered cultured tissue construct which construct seems to comprise the construct of subject-matter (i), wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel, and a second layer of epithelial cells (claims 24-26)

(vii) a method of producing a bilayered cultured skin construct comprising a dermal and an epidermal layer wherein fibroblasts are cultured to form a layer of synthesized extracellular matrix, the extracellular matrix comprising fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, and wherein the cultured skin construct has a basement membrane present at the junction of the first and second layer

(claim 27)

(viii) a method of producing a cultured tissue construct comprising fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar collagen, tenascin and glycosaminoglycans, and wherein the fibroblasts are additionally capable of synthesizing an extracellular matrix on a porous membrane in a culture vessel (claim 29);

and claims 28 and 30 partially, i.e. as far as referring to each of the above identified groups.

3. They are not so linked as to form a single general inventive concept for the following reasons:

The common concept linking together the independent claims is the culturing of fibroblast cells in the absence of exogenous matrix components or synthetic members thereby leading to the formation of a self-supporting extracellular matrix. This is concept is well known from EP-A-0 282.764 (D1, see col.4, line 3 to col.6, line 9).

4. The Applicant requested subject-matter (iv) and (vii) to be subjected to IPE and Applicant payed one additional fee. Hence, claims 16-18, 27 (complete) and claims 28 and 30 partially, i.e. as far as referring to each of the above identified groups are subjected to IPE.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

D1: EP-A-0 282 746

2. Two inventions are subjected to IPE:

subject-matter(iv) concerning a cultured skin which having at least two layers, wherein the first layer is comprised of fibroblast cells, the fibroblast cells contained within the synthesized extracellular matrix layer, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, the extracellular matrix layer comprising fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, the second layer consisting of keratinocytes cells disposed on the first layer, and having a basement membrane present at the junction of the first and second layer (claims 16-18) and

subject-matter (vii) concerning a method of producing a bilayered cultured skin construct comprising a dermal and an epidermal layer wherein fibroblasts are cultured to form a layer of synthesized extracellular matrix, the extracellular matrix comprising fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, the extracellular matrix being produced by the cultured fibroblast cells in the absence of exogenous matrix components or synthetic members, and wherein the cultured skin construct has a basement membrane present at the junction of the first and second layer (claim 27),

and claims 28 and 30 partially, i.e. as far as referring to each of the above identified groups.

3. Novelty (Art.33(2) PCT):

D1 discloses an artificial cultured tissue and its production consisting of one type of cells (see claims 1-15).

In the view of D1 (and of the other cited prior art) the subject-matter of claims 16-18 (subject-matter (iv)) and of claim 27 (subject-matter (vii)) appears novel. The same applies to claims 28 and 30 as far as referring thereto.

4. Inventiveness (Art.33(3) PCT):

It is noted that nowhere in the cited prior art cultured tissues having at least two layers and having a basement membrane present at the junction of the first and second layer have been suggested. In addition, the particular compositions of the first layer which is in the case of subject-matter (iv) fibrillar type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans and in the case of subject-matter (vii) fibrillar type I and type III collagen, decorin, tenascin and glycosaminoglycans, are also not rendered obvious.

Accordingly, the subject-matter of claims 16-18 and 27 comprises an inventive step. The same applies to claims 28 and 30 as far as referring thereto.

Re Item VIII

Certain observations on the international application

The independent claims do not disclose how the particular composition of the first layer can be achieved. Being the basis for the acknowledgement of inventive step, these features are considered essential to the present invention and as such are to be included into the independent claims (Art.6 PCT, lack of clarity).